TREATMENT OPTIONS

FOR

PRIMARY BILIARY CIRRHOSIS (PBC)

Erik Christensen, Copenhagen

Therapy for PBC - Difficulties

- Etiology is uncertain
- Therapies are based on ideas regarding pathogenesis
- Present medical therapies have a limited effect

- Advanced cases: Liver transplantation may be the only option

Randomized clinical trials (RCTs) in PBC

- Relatively few
- Small in size

This means:

- Increased risk of imbalance between groups
- Results not very precise
- Increased risk of type 1 and 2 error
- Increased risk of publication bias

Pathogenetic features of Primary biliary cirrhosis (PBC)

- Destruction of small intrahepatic bile ducts
- ”The florid duct lesion”
- Progressive cholestasis
- Cirrhosis
- Liver failure

Medical therapies for primary biliary cirrhosis (PBC) tested in RCTs.

Therapy	Number of patients in RCT(s)	Effect
Ursodeoxycholic acid (UDCA)	1422	((+))
D-penicillamine	635	-
Colchicine[2]	493	((+))
Cyclosporin A	390	+
Azathioprine	281	+
Malotilate	101	(+)
Methotrexate	99	-
Prednisolone[1]	66	+
Antioxidant supplementation	61	-
Prednisone + Azathioprine[1]	50	+
Budesonide[1]	39	+
Chlorambucil	24	+
Thalidomide	18	-

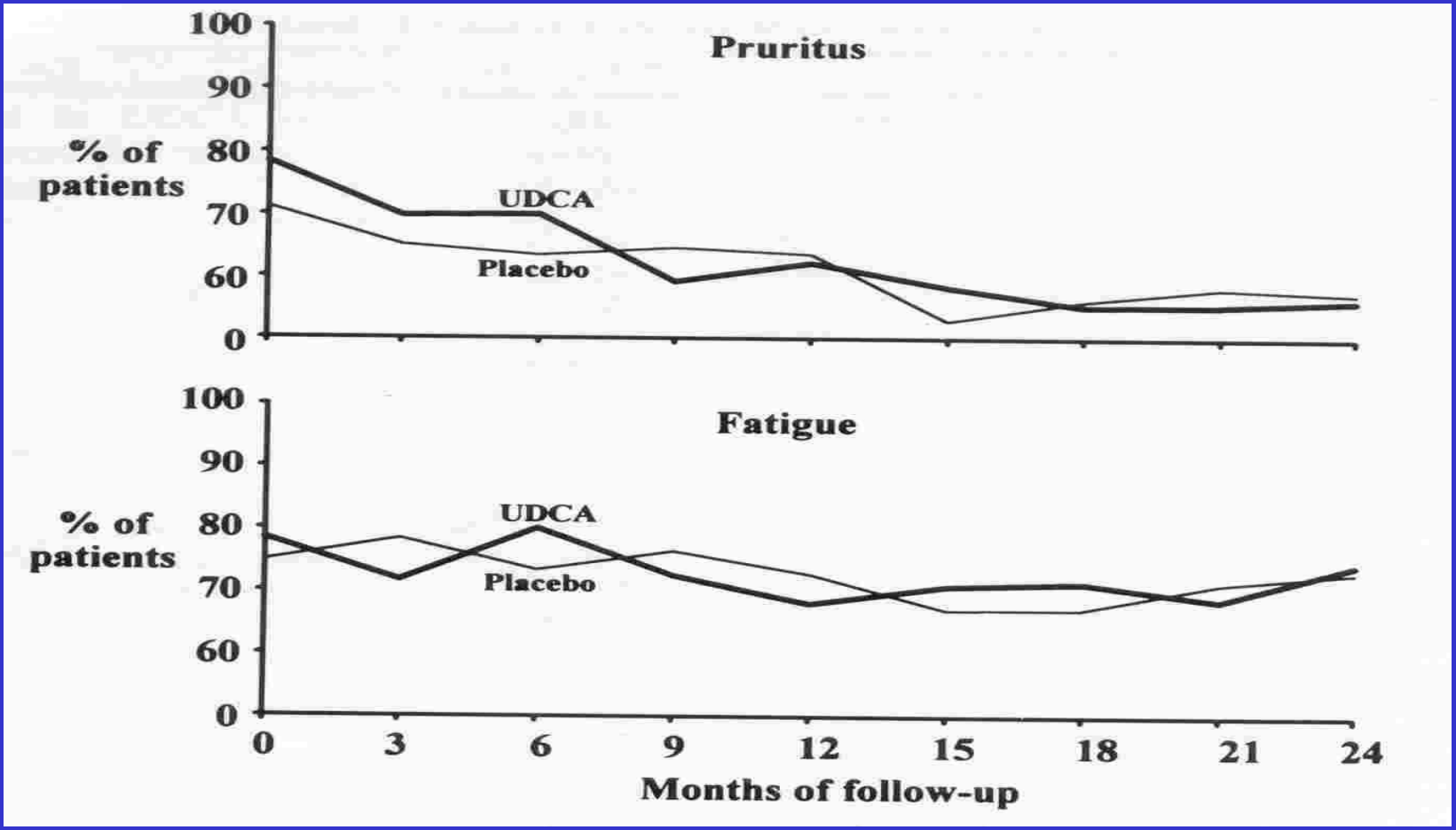
PBC: Ursodeoxycholic acid (UDCA)

Cochrane Database Syst Rev. 2002;(1):CD000551

- Makes the bile ”less toxic”
- UDCA (8-15 mg/kg/day) for 3 months to five years.
- 16 RCTs against placebo (n=15) or no intervention (n=1) in 1422 patients.
- UDCA significantly ($P<0.05$) reduced ascites, jaundice, serum bilirubin and liver enzymes.
- UDCA had no significant effects on mortality, liver transplantation, mortality or liver transplantation, pruritus, fatigue, s-albumin, prothrombin time, quality of life, liver histology, or portal pressure.

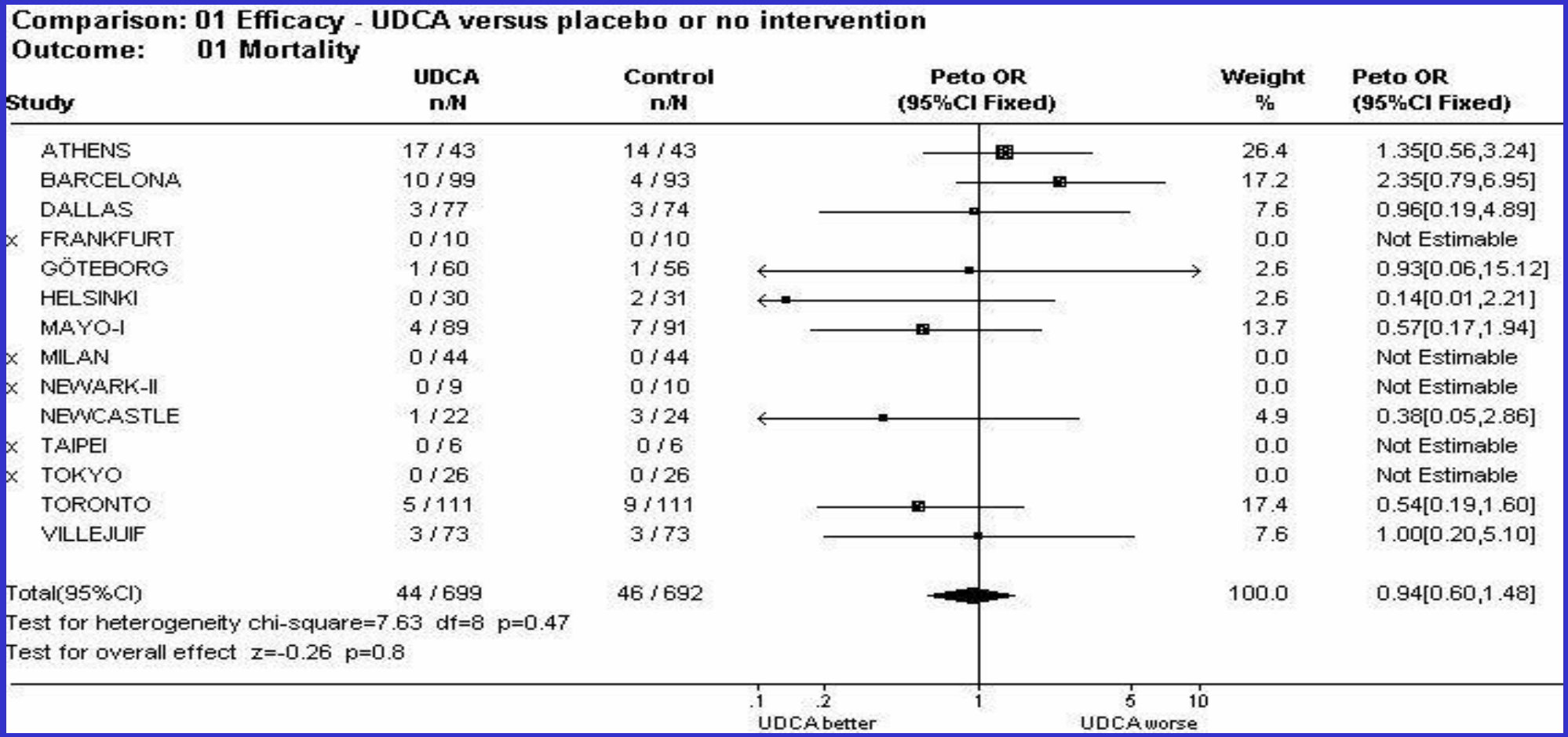
Effect of UDCA on Pruritus and Fatigue

- Heathcote J et al. Hepatology 1994;19:1149-56.
- UDCA (14 mg/kg/day) 111 pts. Placebo 111 pts.



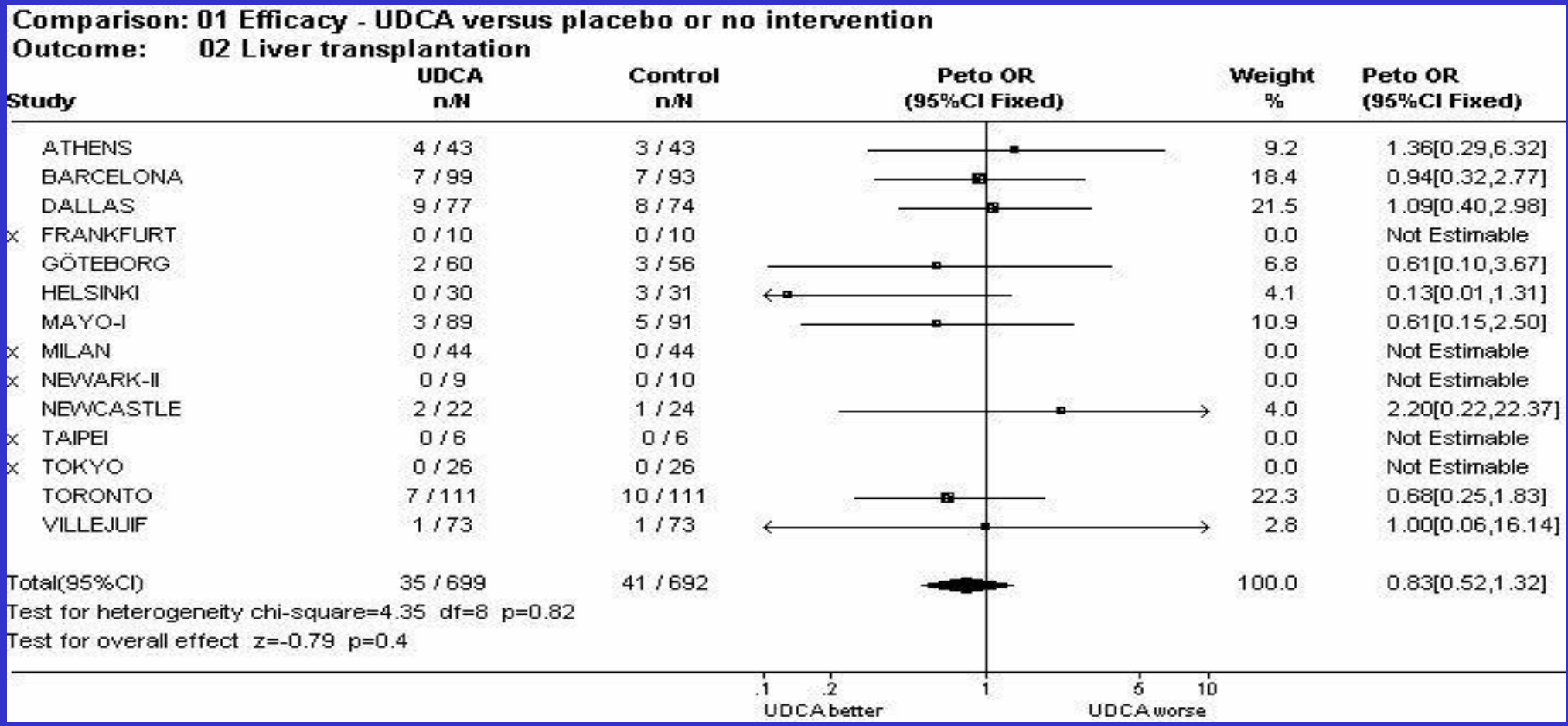
PBC: The effect of UDCA on mortality

Cochrane Database Syst Rev. 2002;(1):CD000551



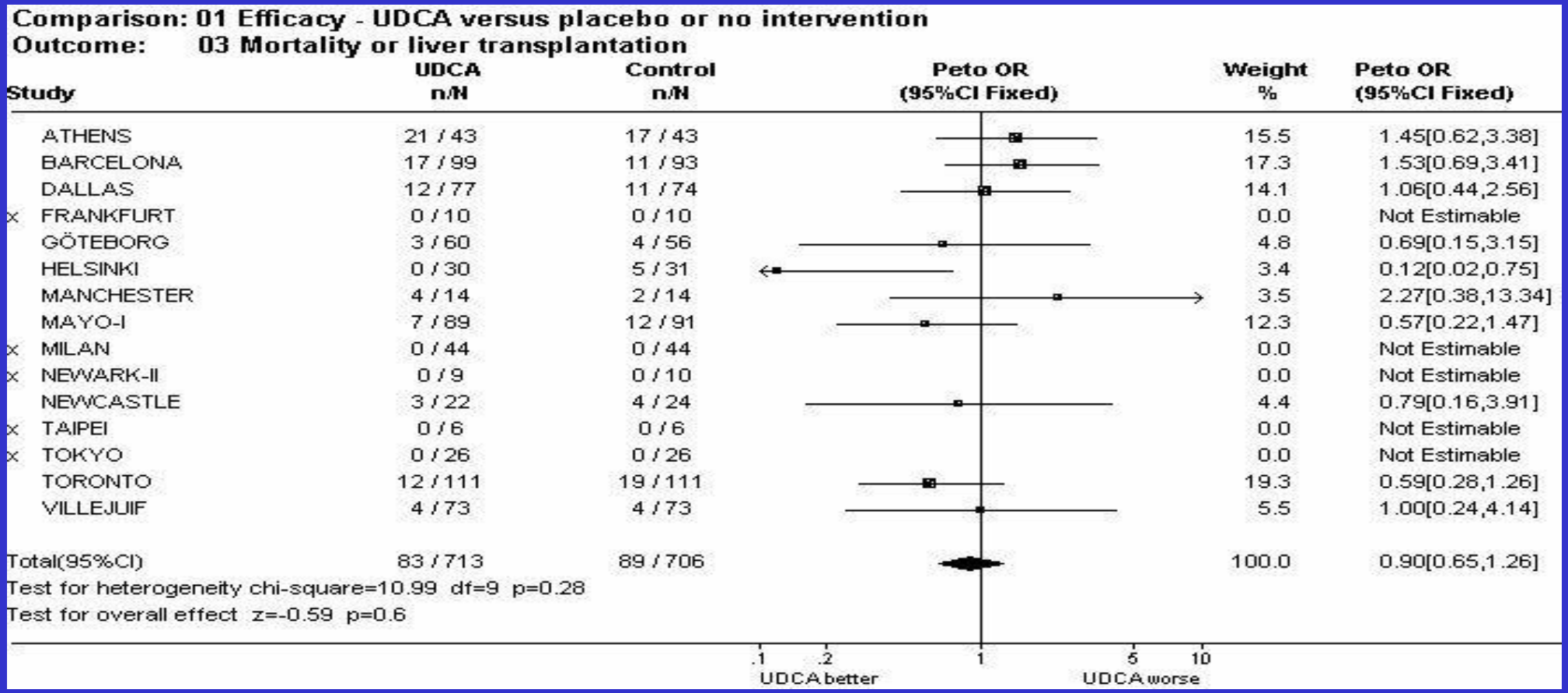
PBC: Effect of UDCA on transplantation

Cochrane Database Syst Rev. 2002;(1):CD000551



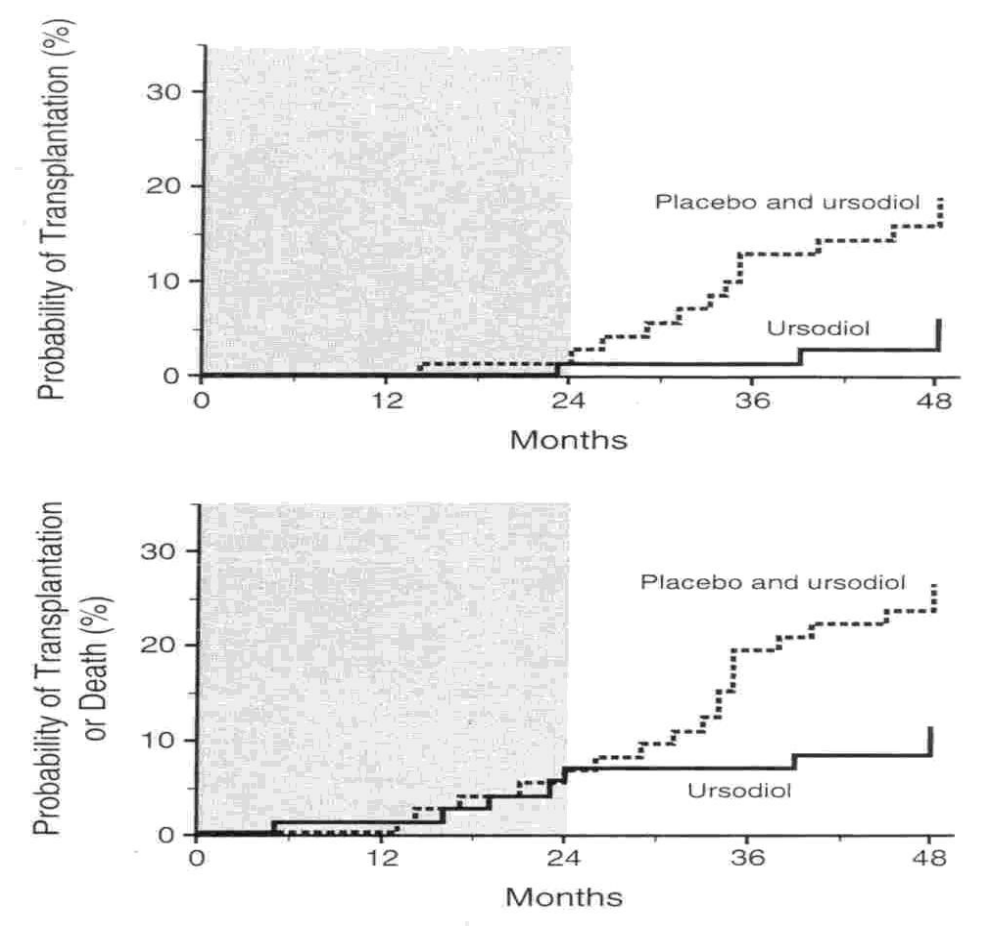
PBC: Effect of UDCA on mortality or transplantation

Cochrane Database Syst Rev. 2002;(1):CD000551



RCT with the largest effect of UDCA

- Poupon R et al. N Engl J Med 1994;330:1342-7.
- Placebo: 72 pts. UDCA (13-15 mg/kg/day): 73 pts.

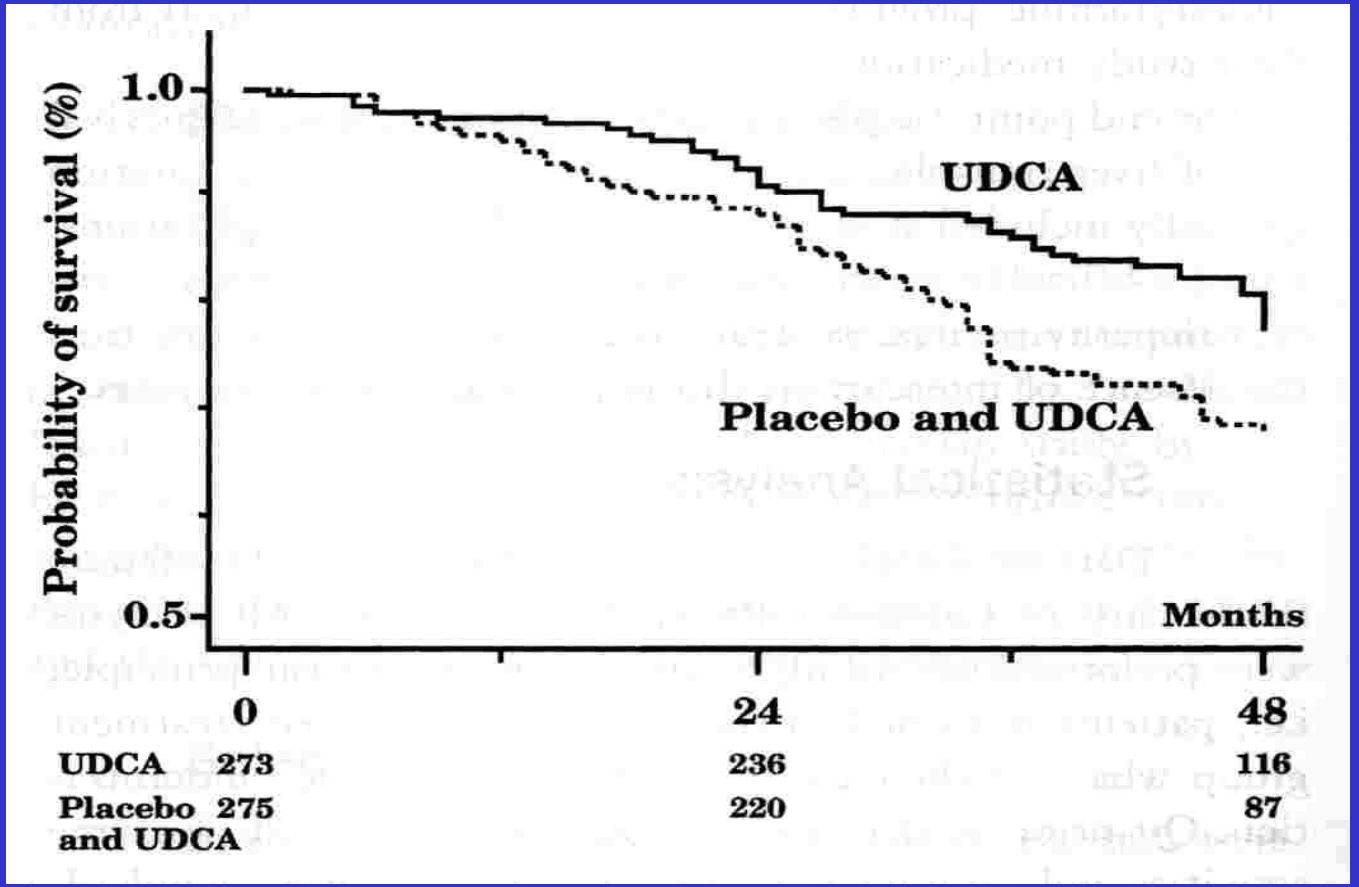


The excess endpoints in the placebo group occurs after ”cross-over”, i.e. **during** UDCA therapy.

The excess endpoints are transplantations, not deaths.

”Cross-over” from Placebo to UDCA after 2 years

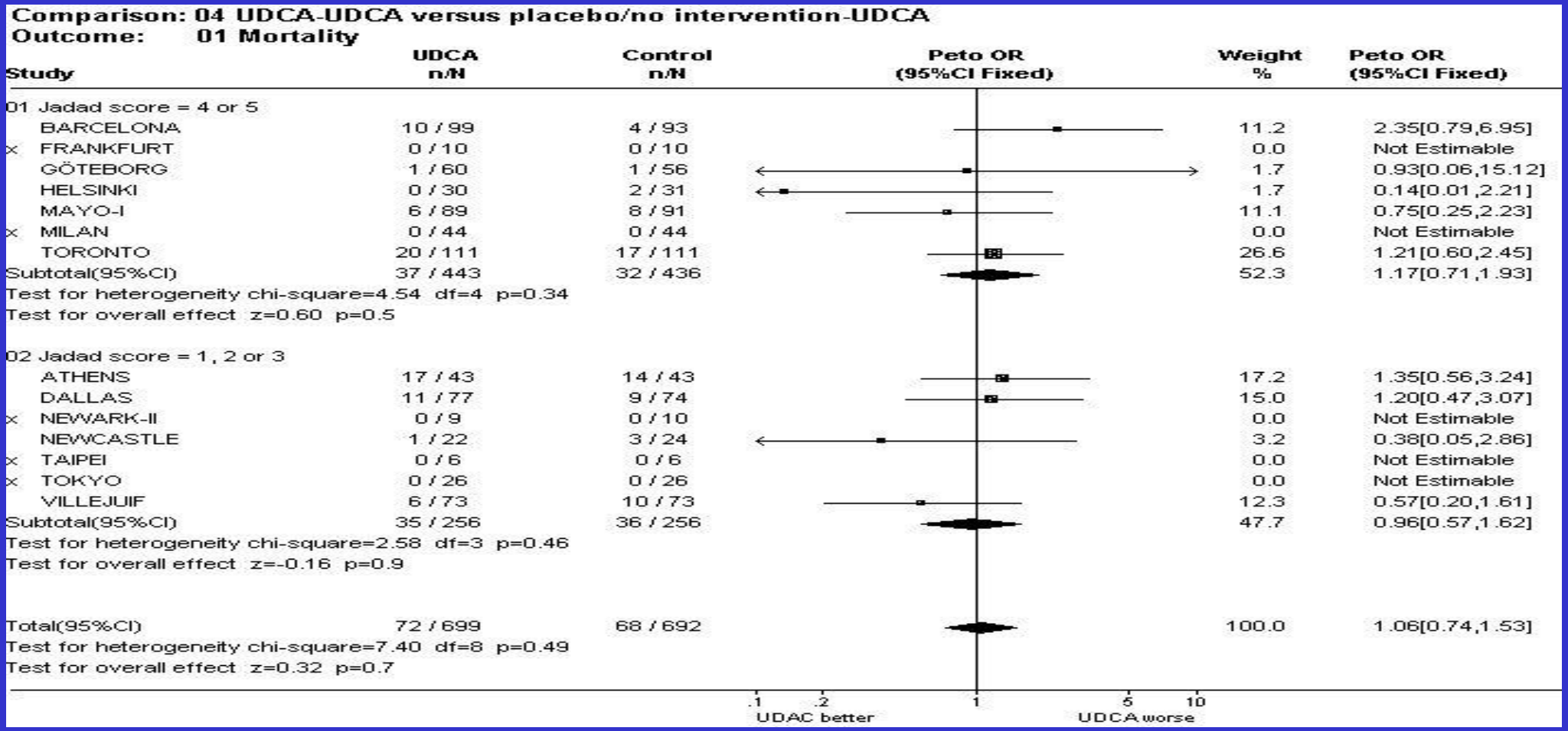
Poupon R et al. Gastroenterology 1997;113:884-90.



The excess endpoints in the Placebo group occurs *during* UDCA treatment

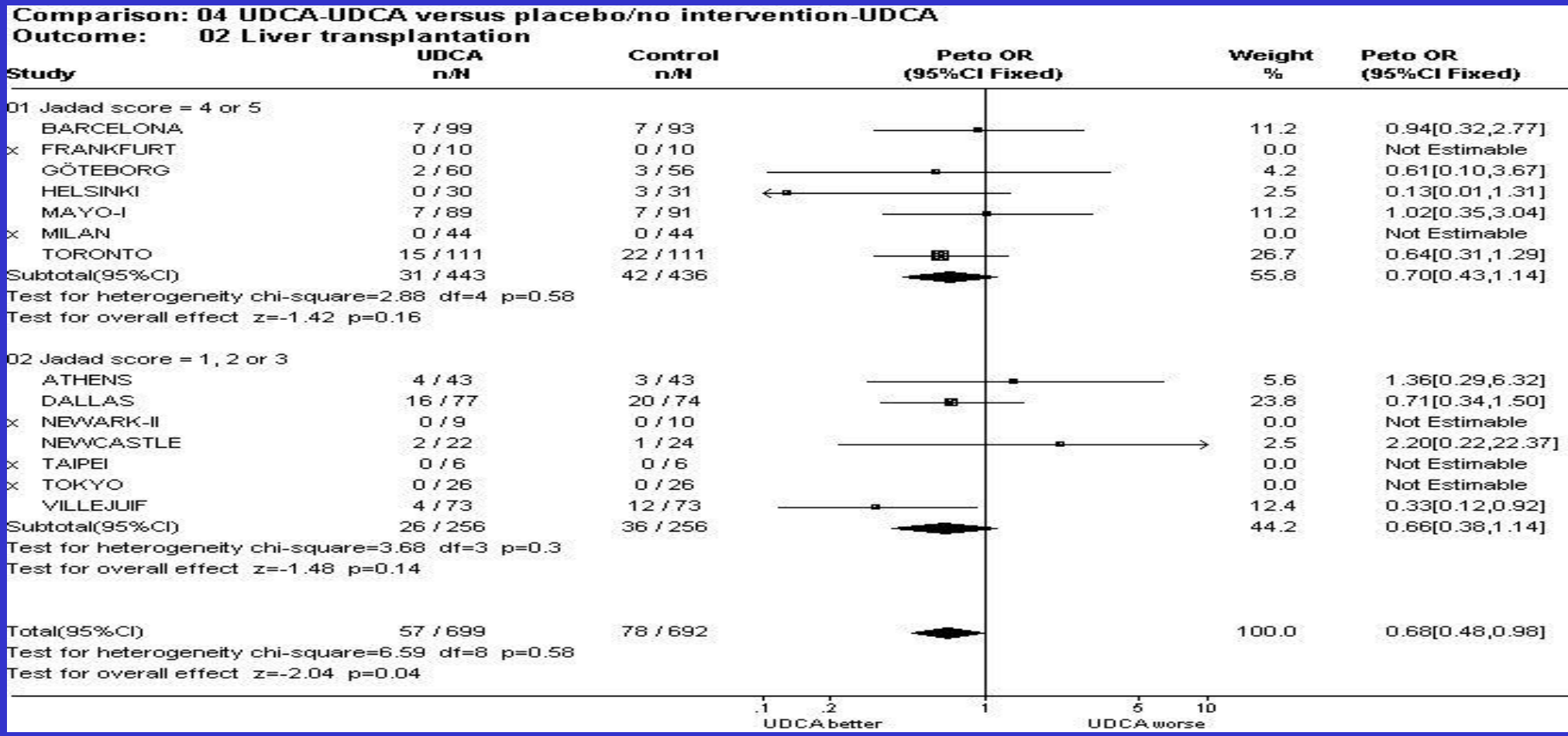
PBC: The effect of UDCA on mortality including ”cross-over” data

Cochrane Database Syst Rev. 2002;(1):CD000551



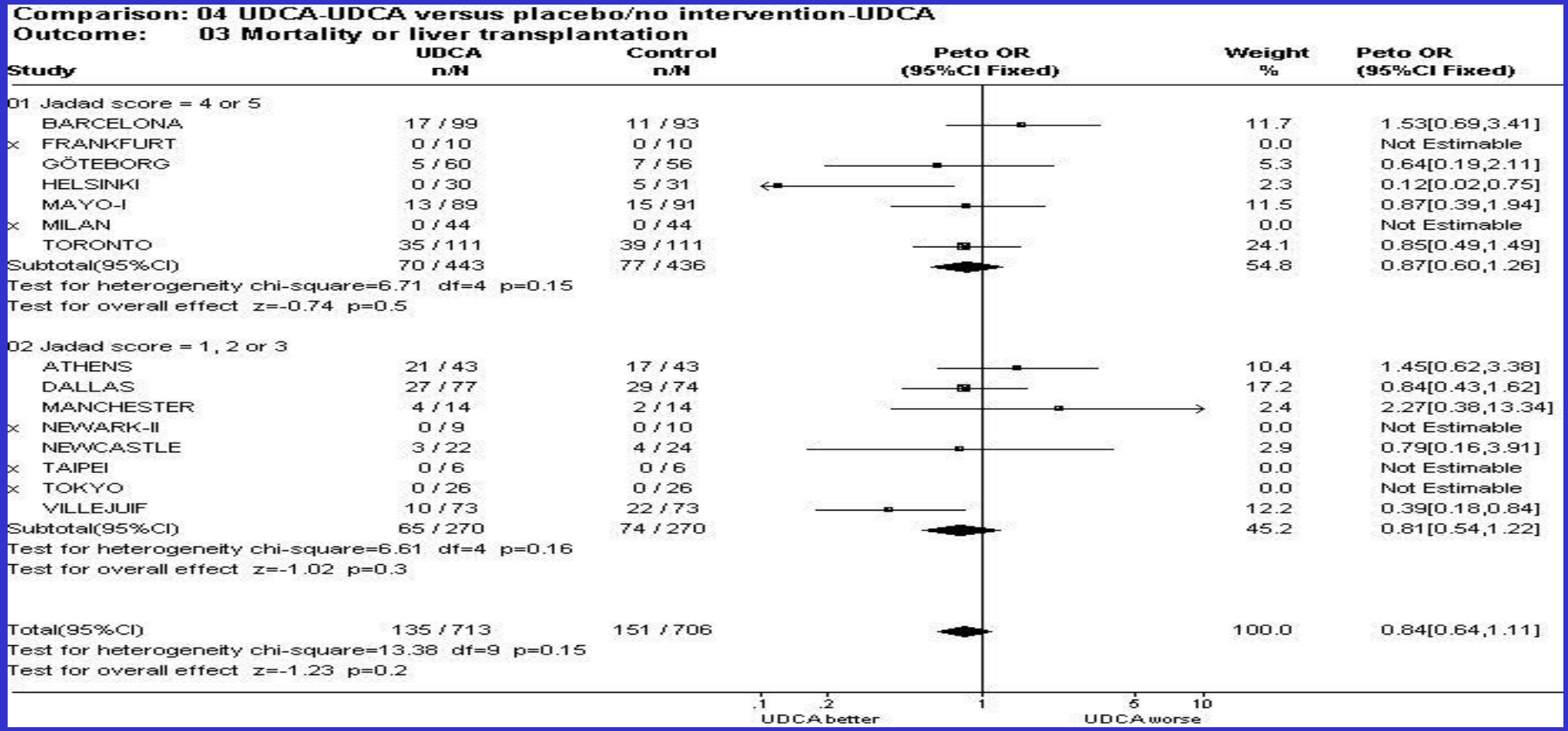
PBC: Effect of UDCA on transplantation including ”cross-over” data

- Cochrane Database Syst Rev. 2002;(1):CD000551



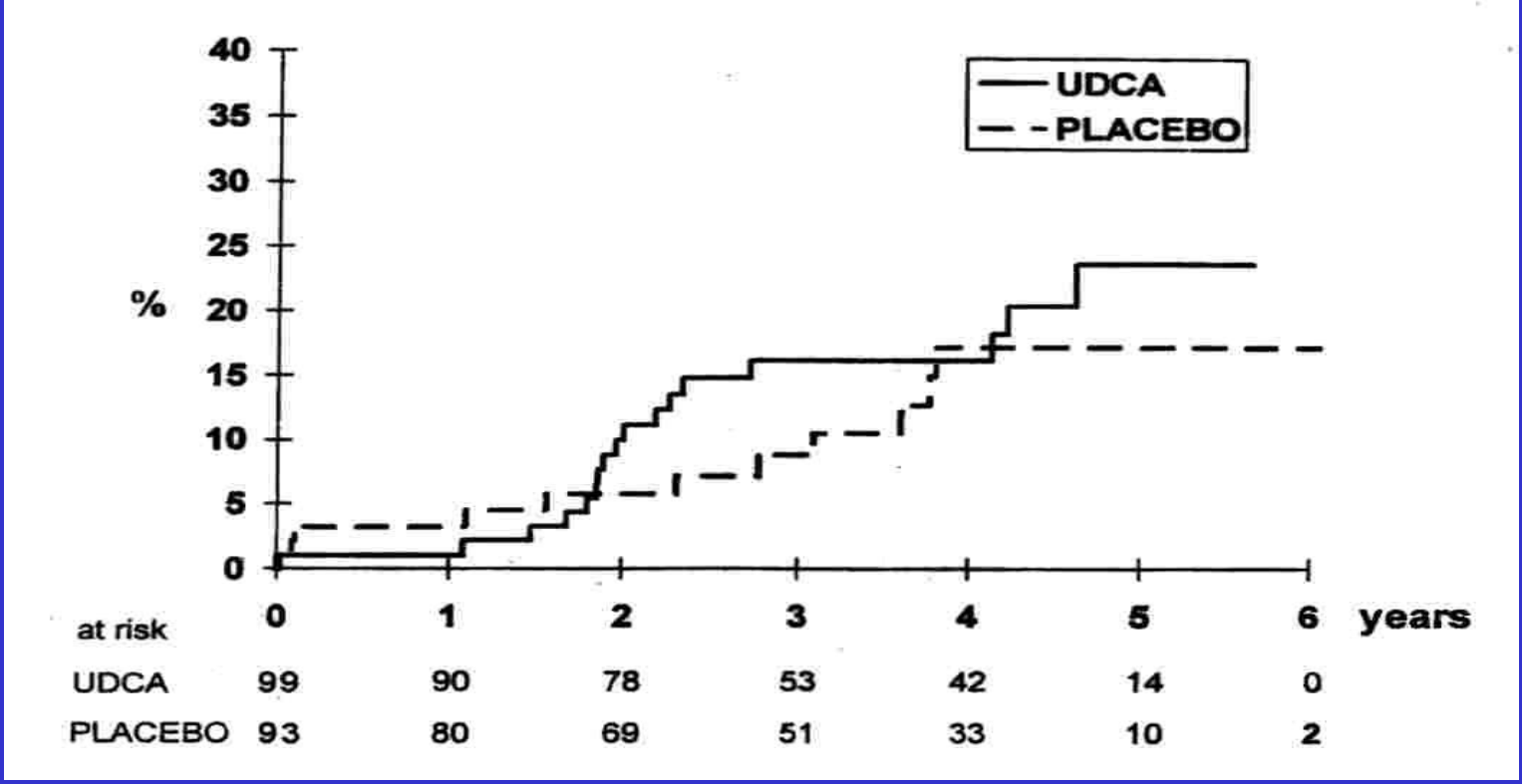
PBC: Effect of UDCA on mortality or transplantation including ”cross-over” data

- Cochrane Database Syst Rev. 2002;(1):CD000551



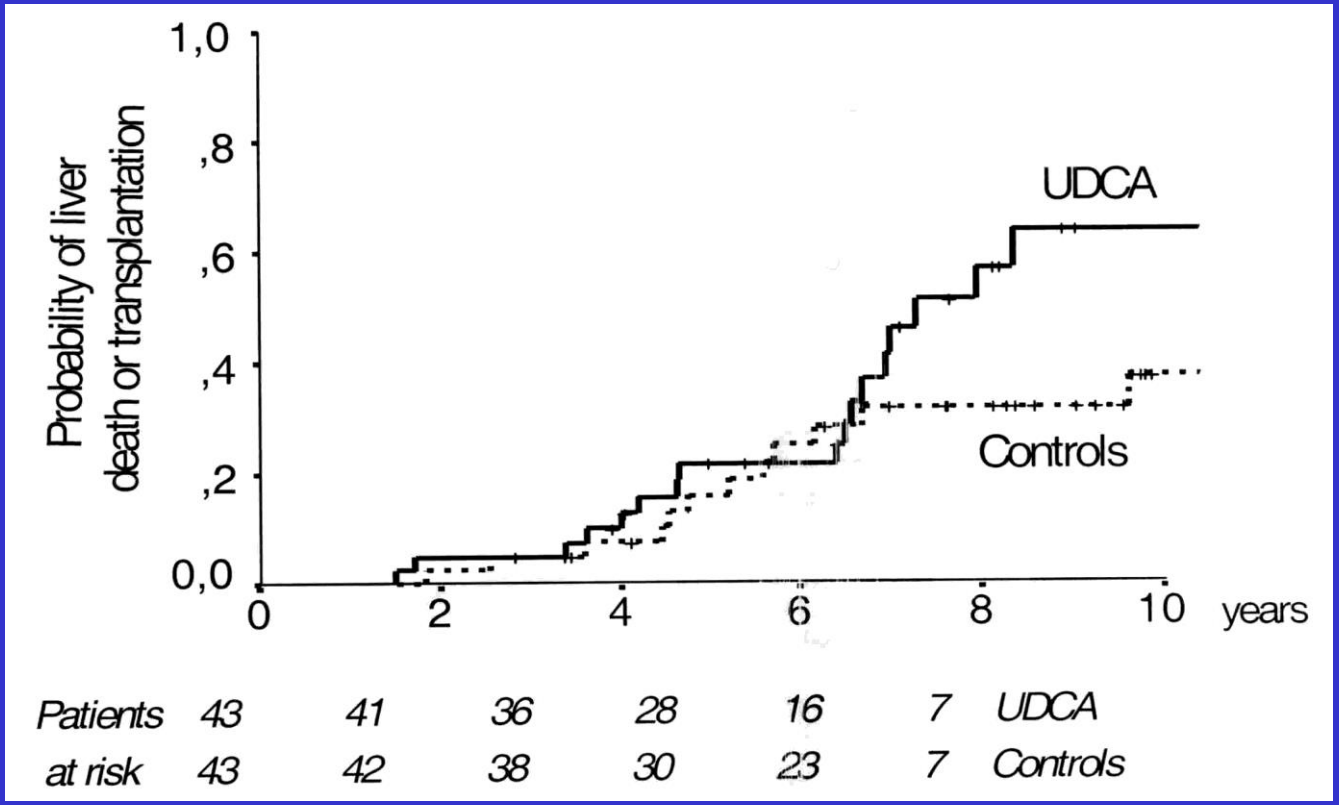
Long term UDCA therapy. Effect on mortality or liver transplantation (1)

- Pares A et al. J Hepatol 2000; 32: 561-66.
- UDCA dose: 14-16 mg/kg/day



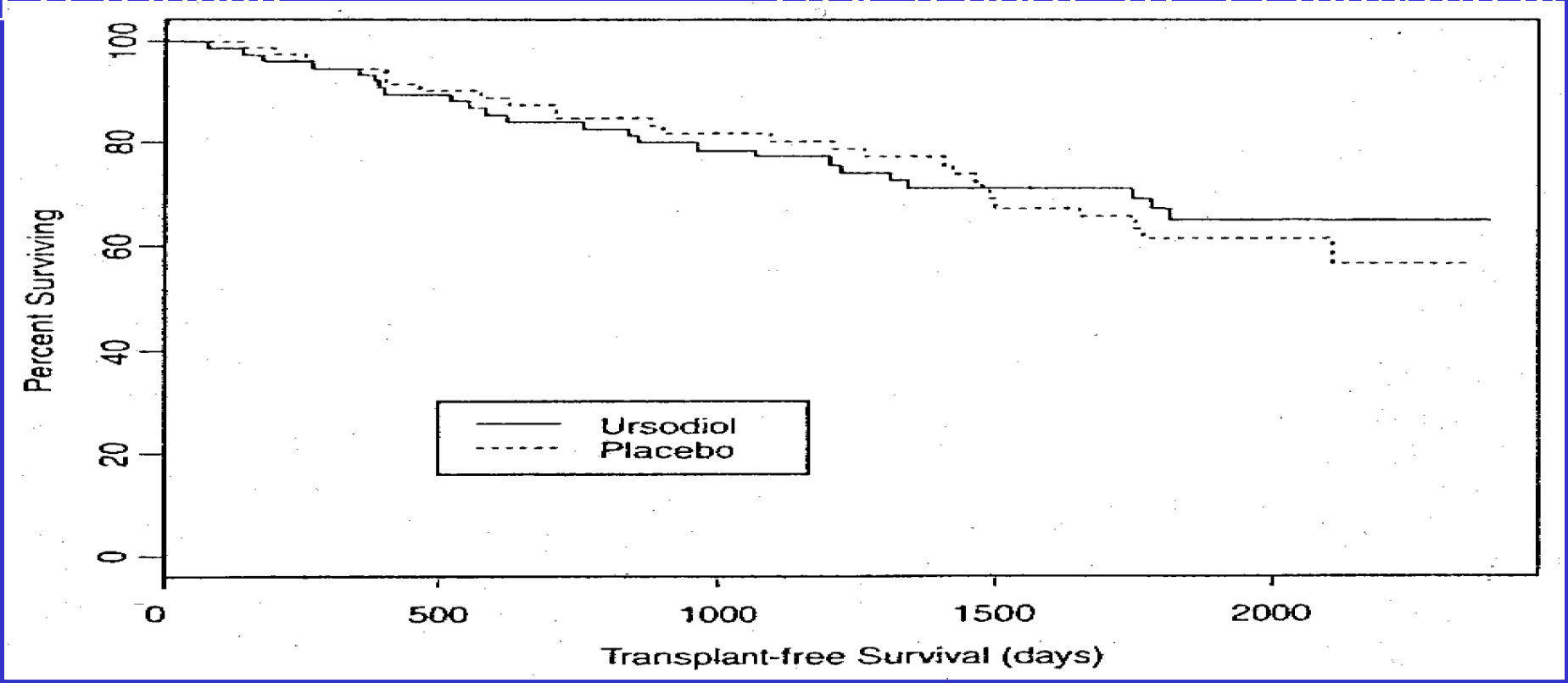
Long term UDCA therapy. Effect on mortality or liver transplantation (2)

- Papatheodoridis G et al. Am J Gastroent 2002;97:2063-70
- UDCA dose: 12 -15 mg/kg/day



Long term UDCA therapy. Effect on mortality or liver transplantation (3)

- Combes B, et al. Am J Gastroent 2004;99:269-70
- 151 patients UDCA dose: 10–12 mg/kg/day



PBC: D-penicillamine vs. placebo

Anti-inflammatory and copper-binding drug

Tested versus placebo or no treatment in 635 patients

Overall no consistent effect was found

The incidence of side effects was high

This drug is no longer used for PBC

PBC: Azathioprine 1-2 mg/kg/day

- **Heathcote** (Gastroenterology 1976;70:656-60)
  22 patients AZA (2 mg/kg/day)
  23 untreated controls

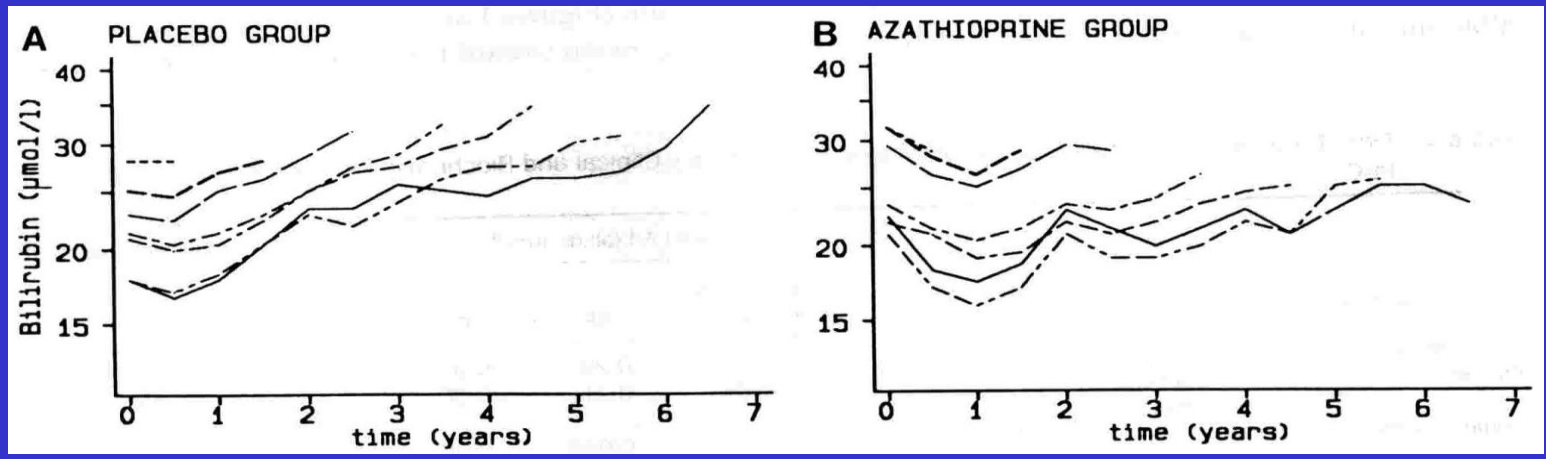
- **Multinational study** (Gastroenterology 1985;89:1084-91)
  124 patients AZA (1 mg/kg/day)
  112 patients placebo

- AZA initially improved symptoms and biochemical tests.
- AZA improved survival slightly in the large study
- Side effects 10% more frequent during AZA.

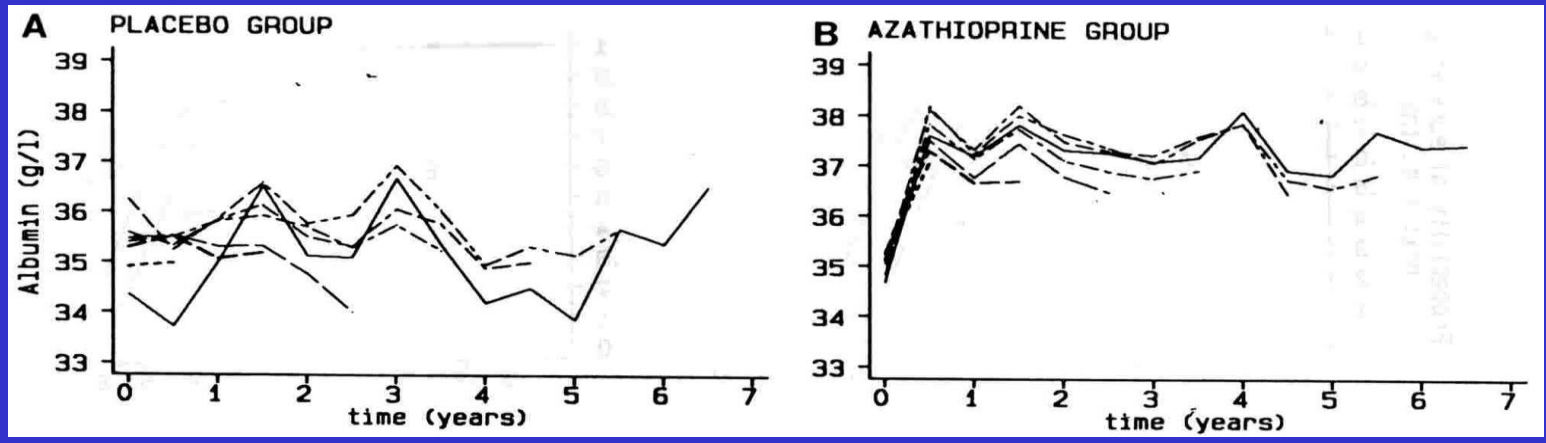
PBC: Effect of Azathioprine

Gastroenterology 1993;105:1865-76

Bilirubin:



Albumin:



PBC: Glucocorticosteroids

A: Mitchison (J Hepatol 1992; 15;336-44)
36 patients **Prednisolone** (30-10 mg/day) vs. placebo for 3 years.

B: Leuschner (J Hepatol 1996;25:29-57)
30 patients: **Prednisolone** (10 mg/day) vs. placebo for 9 months. (All on UDCA)

C: Leuschner (Gastroenterology 1999;117:918-25)
39 patients: **Budesonide k** (9 mg/day) vs. placebo for 2 years. (All on UDCA)

Steroid had significantly beneficial effect on "overall hepatic assessment" (hepatic deaths, doubling of bilirubin, >6 g/l reduction in albumin, new symptoms of portal hypertension and occurrence of cirrhosis) (prednisolone 21% placebo 65%) (A), biochemistry and histology (B and C). No adverse effect was found on bone mineral content.

PBC: Prednisone + Azathioprine

Wolfhagen FH . (J Hepatol 1998; 29:736-42)

50 patients treated for 1 year (all received UDCA).

Prednisone (30-10 mg/day) plus Azathioprine (50 mg/day) vs. Placebo

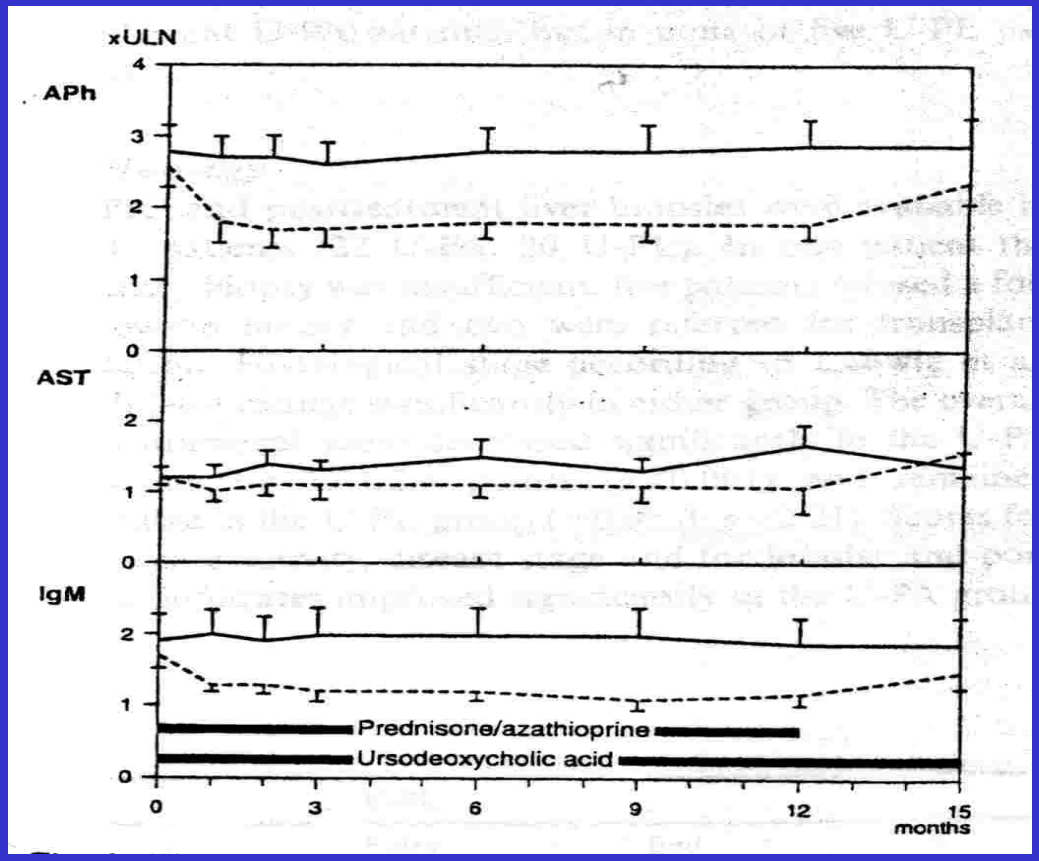
Prednisone + azathioprine led to

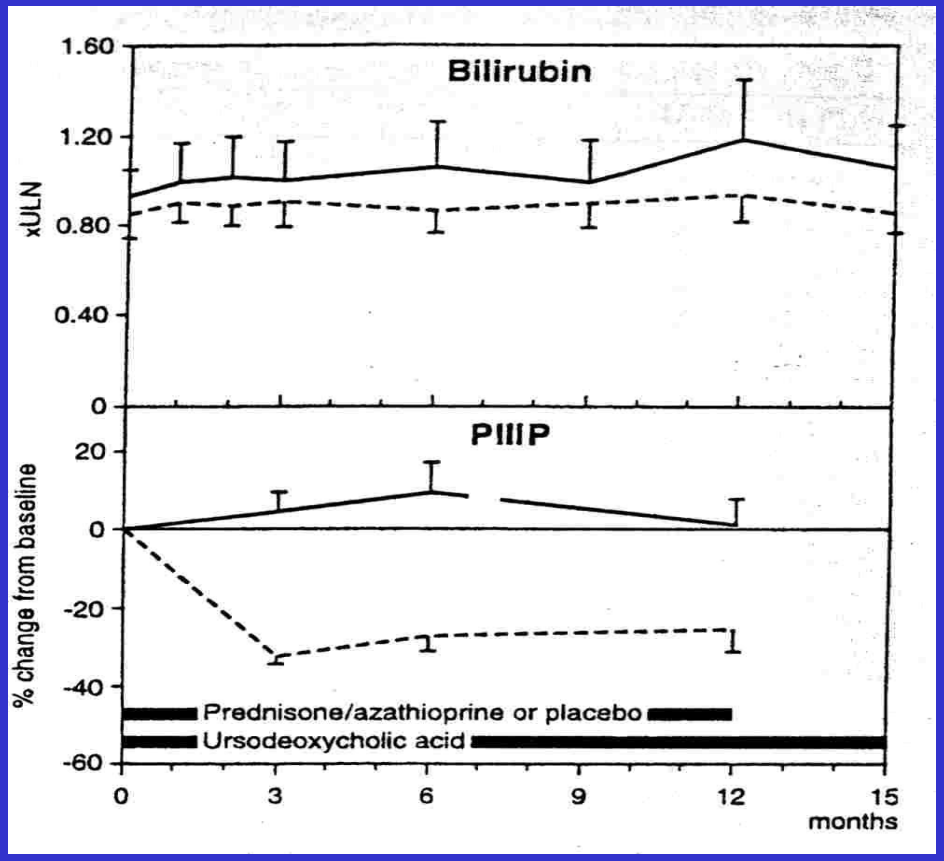
- Less pruritus
- A greater fall in enzymes and IgM
- Less histological disease activity
- Less progression of the histological stage

PBC: Prednisone + Azathioprine

Wolfhagen FH (J Hepatol 1998; 29:736-42)

Pred + Aza + UDCA: dotted line UDCA alone: solid line





PBC: Cyclosporin A (2.5-4 mg/kg/day) versus Placebo

Minuk:	12 patients	(Gastroenterology 1988;95:1356-63)
Wiesner:	29 patients	(N Engl J Med 1990;322:1419-24)
Lombard:	349 patients	(Gastroenterology 1993:104:519-26)

All 3 studies found beneficial effects on liver enzymes and bilirubin.

In the largest study Cyclosporin A significantly improved survival and liver related mortality.

Cyclosporin A significantly reduced kidney function in 9% and caused hypertension in 11%. Close monitoring is necessary.

PBC: Colchicine (1-1.2 mg/day) versus placebo

Without concomitant UDCA therapy

4 RCTs including 241 patients

- Beneficial effects on liver function
- Little effect on histology
- No effect on survival or need for liver transplantation

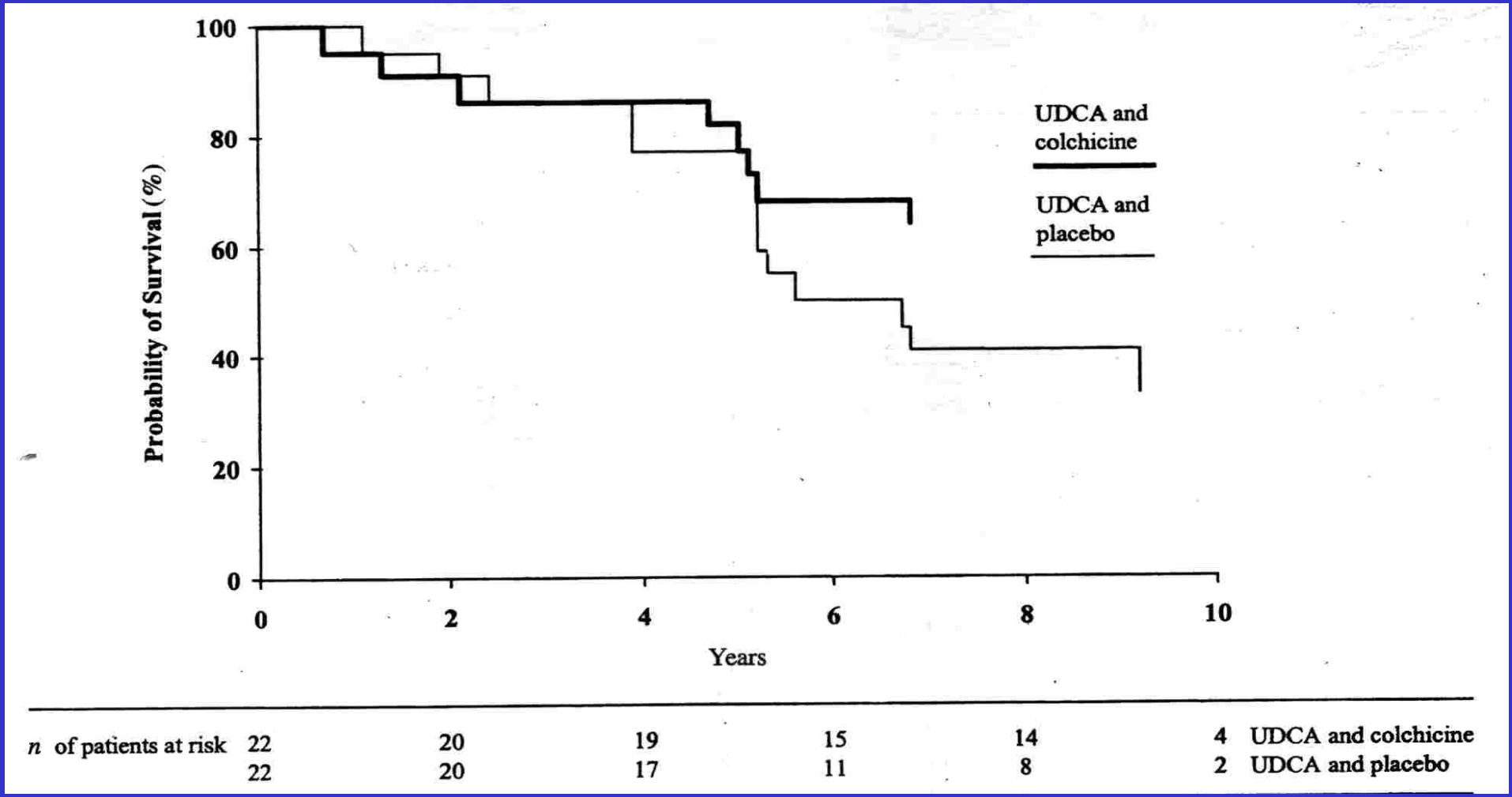
With concomitant UDCA therapy

5 RCTs including 252 patients

- Small beneficial biochemical effect
- Long-term: No slowing of disease progression

PBC: Colchicine vs. Placebo

Battezzati . Aliment Pharmacol Ther 2001;15:1427-34



PBC: Colchicine versus Placebo Cochrane Review

Gong Y, Gluud C. Cochrane Database Syst Rev. 2004;(2):CD004481.

Eleven randomised clinical trials involving 716 patients.

No significant effect on number of

- deaths (colchicine versus control (RR 1.21, 95% CI 0.71 to 2.06)
- deaths and/or liver transplants (RR 1.00, 95% CI 0.67 to 1.49)
- liver complications
- liver biochemical variables
- liver histological measurements

PBC: Methotrexate (7.5-15 mg/week) vs. placebo

A: Hendrickse	60 pts. 6 years	(Gastroenterology. 1999;117:400-7)
B: Gonzalez-Koch	25 pts. (All on UDCA)	(J Hepatol. 1997;27:143-9)
C: Van Steenbergen	14 pts. (All on UDCA)	(Acta Clin Belg 1996;51:8-18)

Results:

A: - Some effect on liver enzymes and immunoglobulins

- No effect on mortality or liver transplantation

B: - No effect on biochemistry or histology

C: - No clinical or histological effect

PBC: Malotilate (1.5 g/day) versus placebo

Multicentre RCT: 101 pt. Mean follow-up: 28 months

(J Hepatol 1993;17:227-35)

Results:

Significant beneficial effects on liver enzymes, IgG and IgM, liver necrosis and inflammatory cell infiltration

No effect on fibrosis, pruritus, disease progression or survival.

The observed benefits appeared too slight to recommend the drug as a single therapy.

PBC: Thalidomide (100 mg/day) versus placebo

McCormick **(J Hepatol 1994;21:496-9)**

Double-blind trial: 18 patients

Results:

- A possible effect on pruritus
- No other effects were found
- Side effects in 40%.

PBC: Antioxidants versus placebo

Prince (Aliment Pharmacol Ther 2003;17:137-41)

Double-blind cross-over trial: 61 patients

Patients received either antioxidants (vitamins A, C, E, selenium, methionine and ubiquinone) or placebo for 3 months. Washout period 1 month.

Results:

- No effect on fatigue or other symptoms
- No effect on liver tests

Medical therapies for primary biliary cirrhosis (PBC) tested in RCTs.

Therapy	Number of patients in RCT(s)	Effect
Cyclosporin A	390	+
Azathioprine	281	+
Prednisolone[1]	66	+
Prednisone + Azathioprine[1]	50	+
Budesonide[1]	39	+
Chlorambucil	24	+
Malotilate	101	(+)
Ursodeoxycholic acid (UDCA)	1422	((+))
Colchicine[2]	493	((+))
D-penicillamine	635	-
Methotrexate	99	-
Thalidomide	18	-
Antioxidants	61	-

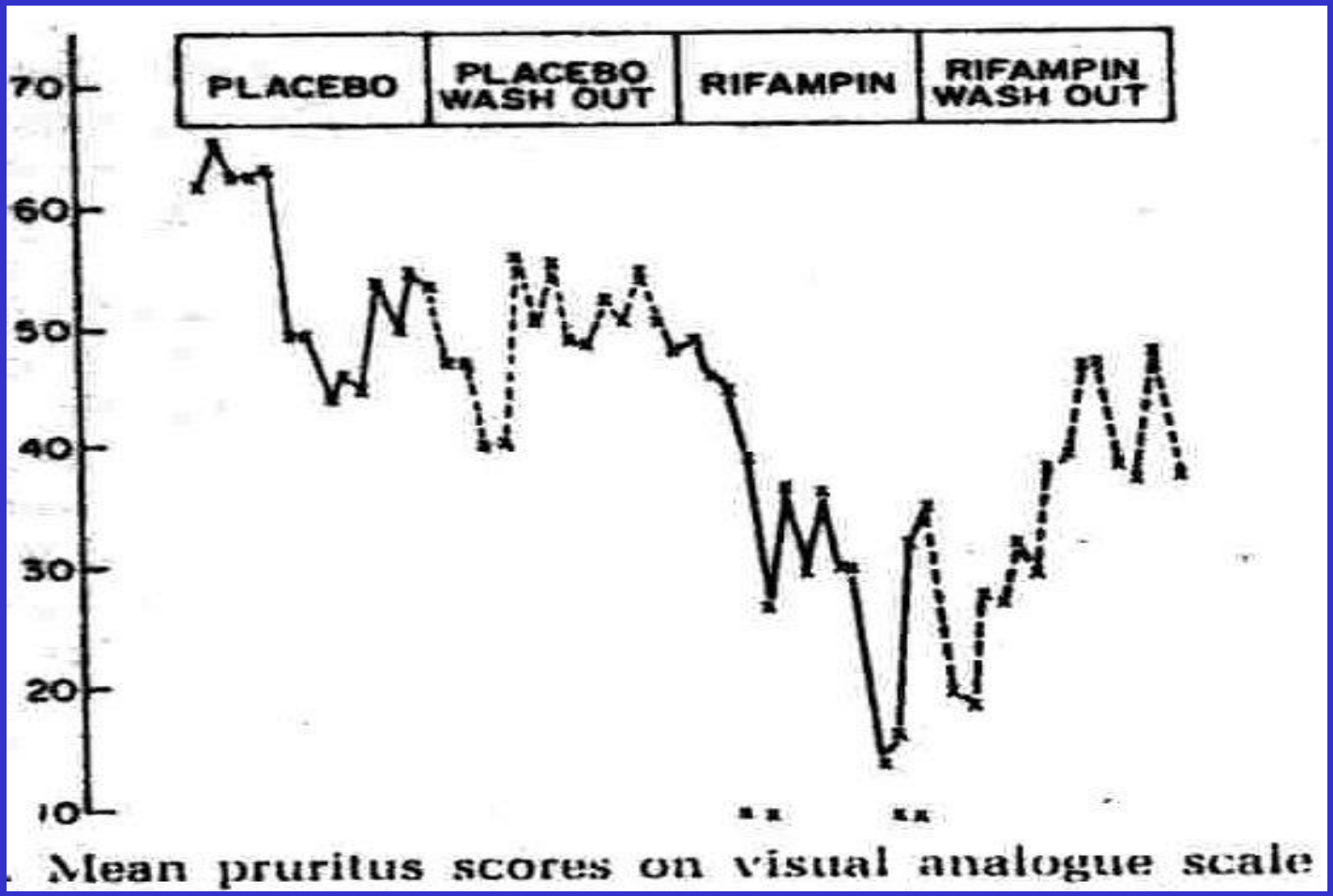
Therapies for pruritus in primary biliary cirrhosis (PBC) tested in RCTs.

Therapy	Number of patients in RCT(s)	Effect
Rifampicin	23	++
Rifampicin (versus Phenobarbitone)	22	+
Diethylaminoethyldextran (DEAE-Dextran)	12	+
Naloxone	8	+
Flumecinol	50	(+)
DEAE-Dextran (versus Cholestyramine)	30	-

Pruritus in PBC: Rifampicin (300-450 mg/day) versus placebo

Ghent

Gastroenterology 1988;94:488-93

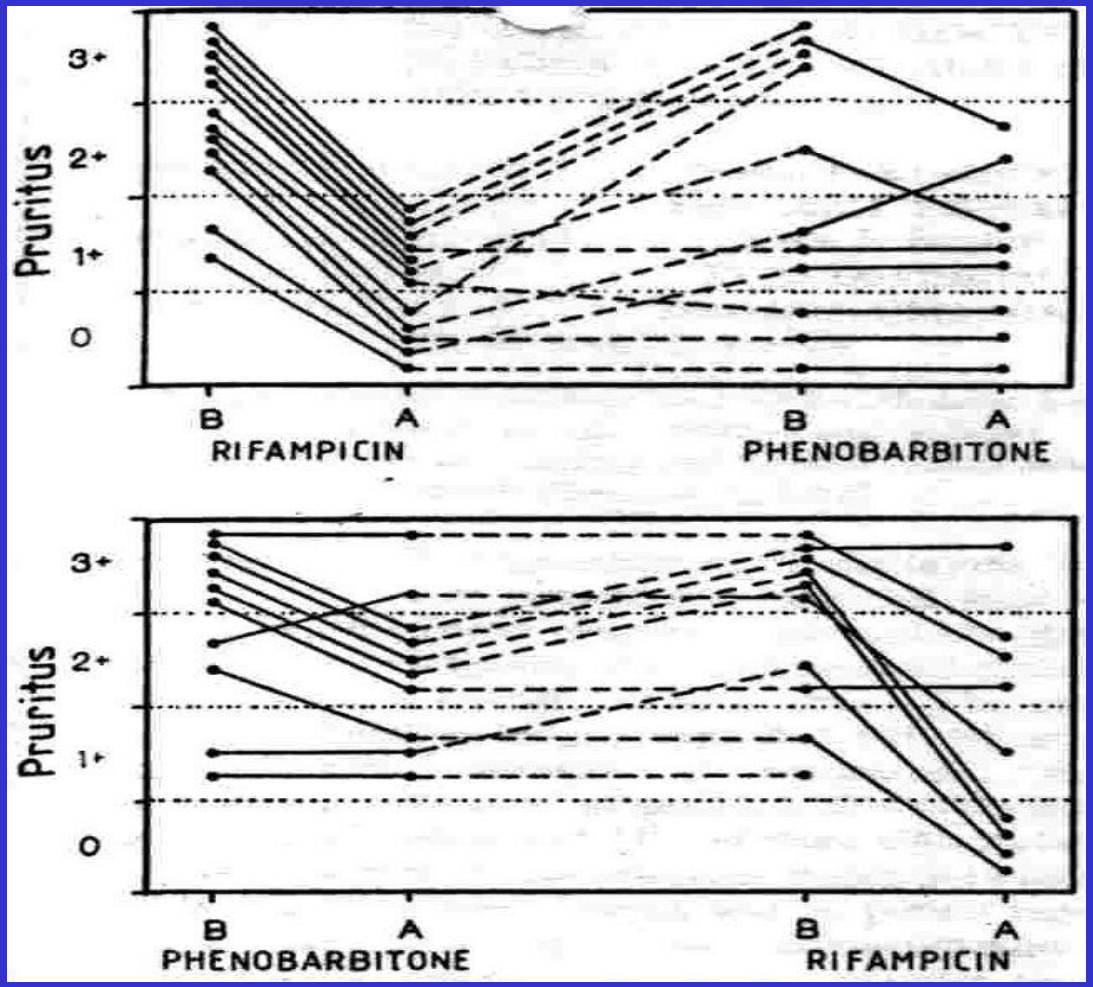


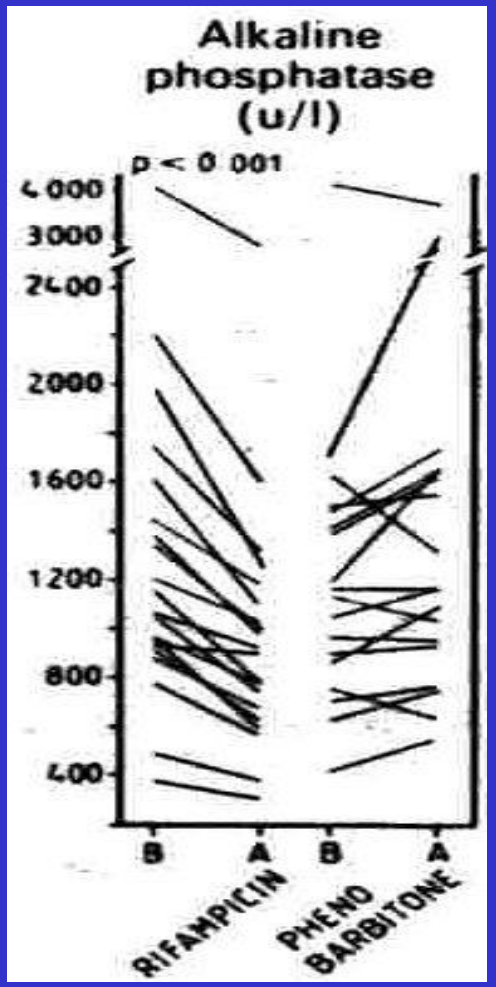
Mean pruritus scores on visual analogue scale

Pruritus in PBC: Rifampicin (10 mg/kg) versus Phenobarbitone (3 mg/kg)

Bachs

Lancet 1989;1:574-6





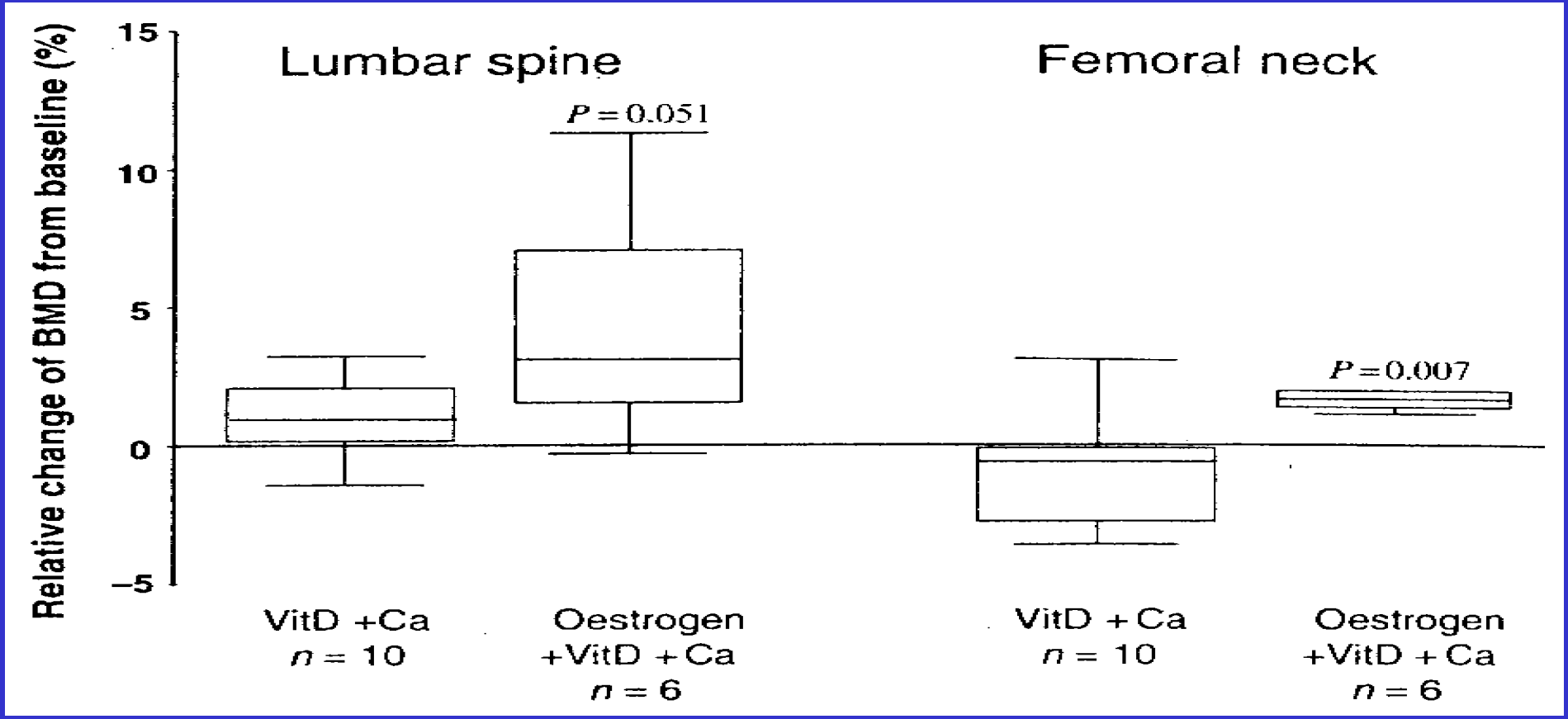
Therapies for osteopenia in primary biliary cirrhosis (PBC) tested in RCTs.

Therapy	Number of patients in RCT(s)	Effect
Transdermal Oestradiol	**60**	**++**
Alendronate (versus Etidronate)	**32**	**++**
Etidronate (versus Sodium flouride)	**32**	**+**
Sodium flouride	**22**	**+**
Etidronate	**12**	**+**
Cyclosporin A	**38**	**+**
Hydroxyapatite	**36**	**+**
Vitamin K2	**30**	**(+)**
Calcium gluconate	**38**	**(+)**
Calcitonin	**25**	**-**
Ursodeoxycholic acid (UDCA)	**88**	**-**

PBC Bone Loss: Transdermal Oestradiol 50 µg/day plus Medroxyprogesterone 2.5 mg/day versus No Hormone

Omarsdóttir 18 patients J Intern Med 2004;256:63-9

2 year RCT. All patients received alfacalcidol 0.25µg/day plus calcium 1 g/day



PBC Bone Loss: Alendronate 10 mg/day versus Etidronate 400 mg/day (2/15 weeks)

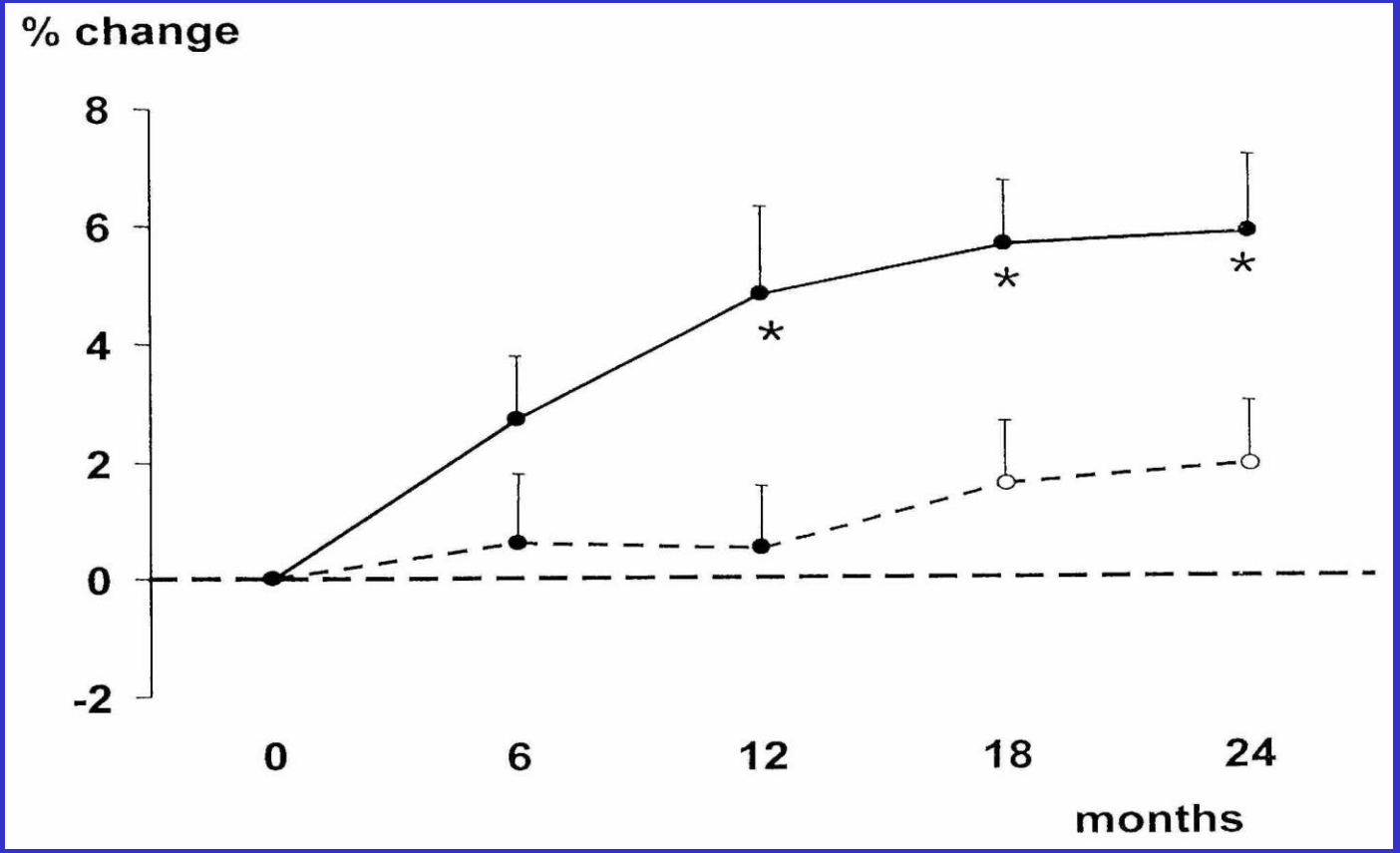
Guañabens 32 patients Am J Gastroenterol 2003;98:2068-74

2 year RCT. All patients received calcium and vitamin D supplementation

Change in lumbar bone mineral density

Alendronate: solid line

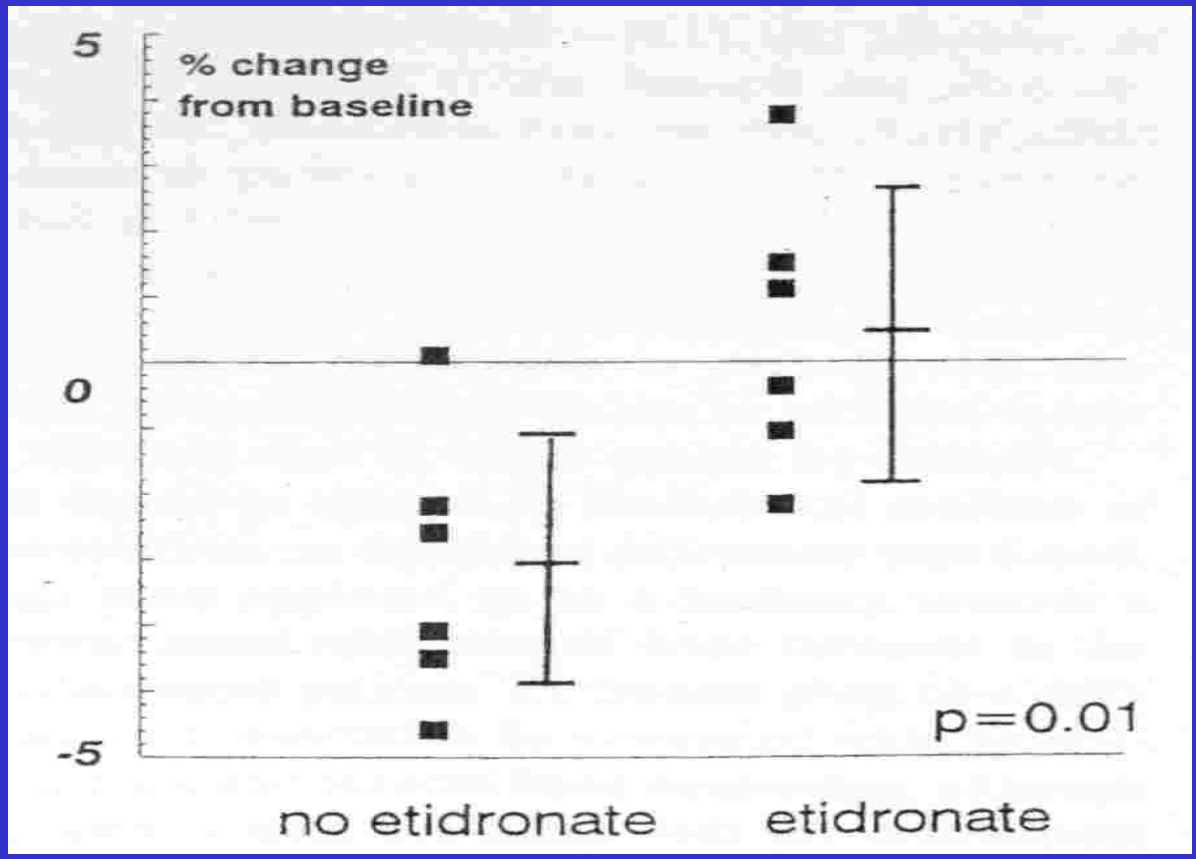
Etidronate: broken line



PBC Bone Loss: Etidronate (400 mg/day 2 of 11 weeks)

Wolfhagen J Hepatol 1997;26:325-30

1 year RCT. All patients received prednisone (~10 mg/day)



Which medical therapies hold most potential in PBC?

General:

- Glucocorticosteroid plus azathioprine

For pruritus:

- Rifampicin

For bone disease:

- Alendronate
- Transdermal oestradiol

Therapy of PBC – Conclusions 1

- Many different therapies have been tested in RCTs
- Highly effective treatments have not been identified
- For late stage disease: transplantation the only option
- Many RCTs are too small to allow a proper evaluation
- Larger multicentre RCTs are needed

PBC therapy – Conclusions 2

- Despite significant effects on some biochemical variables, UDCA has no significantly beneficial effect on symptoms, mortality or the need for liver transplantation.
- More effective (immunosuppressive) therapies (including azathioprine and glucocorticosteroids) should not be withheld from the patients.
- However, even better therapies are needed.
- Better understanding of the etiology is important.
- Gene-technology may be a valuable tool.

ACKNOWLEDGEMENT

Thanks to the staff of the Cochrane Hepato-Biliary Group at the Copenhagen Trial Unit for help in identifying all the performed RCTs.

PBC: Colchicine versus Methotrexate

Kaplan (Gastroenterology 1999;117:1173-80)

Colchicine (1.2 mg/day) 43 patients

Methotrexate (15 mg/week) 42 patients

All on UDCA 2 years follow-up

Both led to decrease in pruritus and liver enzymes

Only Methotrexate improved histology and IgG

Neither drug had effect on bilirubin or albumin.

Five patients receiving Methotrexate (and none on Colchicine) developed interstitial pneumonitis.